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EXAMINER	
STAPLES, MARK	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/573,134	STEINBERG ET AL.	
	Examiner	Art Unit	
	MARK STAPLES	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08/25/2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,9 and 11-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,9 and 11-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment of claims 1, 9, and 11 and the cancelation of claim 7 in the paper filed on 08/25/2009 is acknowledged.

Claims 1-6, 9, and 11-14 are pending and at issue.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Objections and Rejections that are Withdrawn

Canceled Claim Rejections Moot / Withdrawn

2. The objection and rejections of canceled claim 7 are moot and therefore are withdrawn.

Objection Withdrawn

3. The objection to claims 1 and 9 is withdrawn as Applicant has overcome this objection through claim amendment.

Claim Rejections Withdrawn - 35 USC § 112 Second Paragraph

4. The rejection of claims 1 and 9 for unclear recitation of alternative primers is withdrawn as Applicant has amended the claims to clearly recite which primers are claimed or claimed in the alternative.

5. The rejection of claims 1-6 and 12-14 as being incomplete for omitting essential steps is withdrawn as Applicant has amended the claims to recite a step of detection and has pointed ot specification for support of this step.

6. The rejection of claim 9 for reciting an improper Markush group recitation is withdrawn as Applicant has amended the claim to recite a proper Markush group.

Claim Rejections Withdrawn - 35 USC § 103(a)

7. The rejection of claims 9 and 11 under 35 U.S.C. 103(a) as being unpatentable over Kmiec et al. (WO200173002 published 2001) and Buck et al. (1999) is withdrawn. Applicant's arguments have been considered but are moot in view of the new ground(s) of rejection, necessitated by claim amendment.

8. The rejection of claims 9 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber et al. (WO200118252 published 2001), Buck et al. (1999), and Stratagene (1988 catalog) is withdrawn. Applicant's arguments have been considered but are moot in view of the new ground(s) of rejection, necessitated by claim amendment.

9. The rejection of claims 9 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ferrie et al. (GB2327497 published 1999) and Buck et al. (1999) is withdrawn. Applicant's arguments have been considered but are moot in view of the new ground(s) of rejection, necessitated by claim amendment.

10. The rejection of claims 9 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Coste et al. (1998), Nollet et al. (1996), Buck et al. (1999), and

Stratagene (1988 catalog) is withdrawn. Applicant's arguments have been considered but are moot in view of the new ground(s) of rejection, necessitated by claim amendment.

11. The rejection of claims 9 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Albertsen et al. (United States Patent 6,114,124 issued 2000) and Buck et al. (1999) is withdrawn. Applicant's arguments have been considered but are moot in view of the new ground(s) of rejection, necessitated by claim amendment.

12. The rejection of claims 9 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ikawa et al. (1988), and Buck et al. (1999) is withdrawn. Applicant's arguments have been considered but are moot in view of the new ground(s) of rejection, necessitated by claim amendment.

13. The rejection of claims 1, 4-6, and 14 under 35 U.S.C. 103(a) as being unpatentable over Salahshor et al. (1999, previously cited), Davies et al. (June 2002), Kmiec et al. (WO200173002 published 2001), Shuber et al. (WO200118252 published 2001), Ferrie et al. (GB2327497 published 1999), Coste et al. (1998), Nollet et al. (1996), Albertsen et al. (United States Patent 6,114,124 issued 2000), Ikawa et al. (1988), and Buck et al. (1999).

14. The rejection of claim 2 under 35 U.S.C. 103(a) as being unpatentable over Salahshor et al. (1999, previously cited), Davies et al. (June 2002), Kmiec et al. (WO200173002 published 2001), Shuber et al. (WO200118252 published 2001), Ferrie et al. (GB2327497 published 1999), Coste et al. (1998), Nollet et al. (WO2002058534 published 1 August 2002), Albertsen et al. (United States Patent 6,114,124 issued

2000), Ikawa et al. (1988), and Buck et al. (1999) as applied to claim 1 above, and further in view of Gerry et al. (1999) is withdrawn. Applicant's arguments have been considered but are moot in view of the new ground(s) of rejection, necessitated by claim amendment.

15. The rejection of claim 3 under 35 U.S.C. 103(a) as being unpatentable over Salahshor et al. (1999, previously cited), Davies et al. (June 2002), Kmiec et al. (WO200173002 published 2001), Shuber et al. (WO200118252 published 2001), Ferrie et al. (GB2327497 published 1999), Coste et al. (1998), Nollet et al. (WO2002058534 published 1 August 2002), Albertsen et al. (United States Patent 6,114,124 issued 2000), Ikawa et al. (1988), and Buck et al. (1999) as applied to claim 1 above, and further in view of Shuber et al. (WO199858081 published 1998) is withdrawn. Applicant's arguments have been considered but are moot in view of the new ground(s) of rejection, necessitated by claim amendment.

16. The rejection of claims 12 and 13 under 35 U.S.C. 103(a) as being unpatentable over Salahshor et al. (1999, previously cited), Davies et al. (June 2002), Kmiec et al. (WO200173002 published 2001), Shuber et al. (WO200118252 published 2001), Ferrie et al. (GB2327497 published 1999), Coste et al. (1998), Nollet et al. (WO2002058534 published 1 August 2002), Albertsen et al. (United States Patent 6,114,124 issued 2000), Ikawa et al. (1988), and Buck et al. (1999) as applied to claim 1 above, and further in view of Baba et al. (1996) is withdrawn. Applicant's arguments have been considered but are moot in view of the new ground(s) of rejection, necessitated by claim amendment.

New Rejections Necessitated by Amendment

New Claim Rejections - 35 USC § 112, First Paragraph

17. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

18. Claims 1-6, 9, and 11-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 1 and 9 newly recite pathway as follows: " . . .by means of mutational analysis of two genes of each of two different signaling pathways, where the genes for the first pathway are APC, K-ras, and the genes for the second pathway are β-catenin and B-raf ". Support for these two pathways is not found in the specification.

It is noted that support for two pathways are given but are not the pathways recited in the instant claims. These pathways are given below:
"[0029] . . . The signal pathways covered by the markers integrated in this method are the wnt signal pathway and the MAPK signal pathway. Components of the method are the markers APC, on the one hand, and β-catenin, on the other hand, from the wnt signal pathway, together with the markers K-ras, on the one hand, and B-raf, on the other hand, from the MAPK signal pathway. This combination of two markers from the

wnt signal pathway, together with the two markers from the MAPK signal pathway, allows reliable diagnosis of colon carcinoma."

New Claim Rejections - 35 USC § 103

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

21. Claims 1, 4-6, 9, 11, and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Salahshor et al. (1999, previously cited), Davies et al. (June 2002, previously cited), Kmiec et al. (WO200173002 published 2001, previously cited), Shuber et al. (WO200118252 published 2001, previously cited), Ferrie et al. (GB2327497 published 1999, previously cited), Coste et al. (1998, previously cited), Nollet et al.

(1996, previously cited), Albertsen et al. (United States Patent 6,114,124 issued 2000, previously cited), Ikawa et al. (1988, previously cited), McCormick (1999), Buck et al. (1999, previously cited), and Stratagene (1988).

Claim Interpretation

Claims 1 and 9 newly recite primers targeting genes of two pathways. The specific pathways recited in the claims are not supported by the specification (see above) and are not found in the art. However, pathways having the recited genes are well known in the art as taught by McCormick (1999) as given below. The pathways taught by McCormick are also found in the instant specification. Thus the claims are reasonably interpreted as being directed to these known pathways so that the applicability of the prior art can be determined.

Regarding claims 1, 9, and 11, Salahshor et al. teach methods for the non-invasive early detection of colon cancer or intestinal cancer precursor cells (entire publication) by means of mutational analysis of the genes for APC, K-ras, and β-catenin in a sample (see Table 1), characterized in that the method comprises the following steps:

obtaining DNA from the sample (see the section *DNA extraction* on p. 248),

performing an amplification reaction in the genes for APC, K-ras, and β-catenin, using primers to the genes for APC, K-ras, and β-catenin (see last paragraph on p. 248 continued through the 3rd full paragraph on p. 249),

wherein amplification products are formed and performing a mutational analysis in the

amplification products (entire article, especially Table 1).

Regarding claims 1, 9, and 11, Salahshor et al. teach obtaining DNA but do not specifically teach collecting a stool sample and homogenizing the sample to obtain the DNA; do not specifically teach the B-raf gene; and do not specifically teach primers consisting of sequences of instant SEQ ID NOs; 1-18. Salahshor et al. teach pathways (see last paragraph on p. 251) but do not specific teach two pathways of at least two genes each. Regarding claims 9 and 11, Salahshor et al. do not specifically teach kits.

Regarding claims 1, 9, and 11, Ikawa et al. teach methods for the non-invasive early detection of cancer by means of mutational analysis of the genes for B-raf in a sample (entire article, especially the Title) and for the ras gene family (see 1st sentence on p. 2651), and teach kitys (see 3rd sentence of the 2nd paragraph on p. 2651) characterized in that the method comprises the following steps:
obtaining DNA from the sample (see 2nd paragraph on p. 2651),
performing an amplification reaction by synthesizing DNA in the genes for B-raf using primers (see Figure 1 and legend) and teach sequences comprising sequences of instant SEQ ID NOs: 17 and 18,
wherein amplification products are formed and performing a mutational analysis in the amplification products (entire article especially Figure 1).

Regarding claims 1, 9, and 11, Ikawa et al. teach detection of cancer and teach obtaining DNA but do not specifically teach collecting a stool sample and homogenizing the sample to obtain the DNA; do not specifically teach detection of colon cancer or

intestinal cancer; do not specifically teach the APC and β-catenin genes; and do not teach sequences comprising sequences of instant SEQ ID NOs: 1-16. Ikawa et al. do not specifically teach pathways.

Regarding claims 4 and 5, Ikawa et al. teach separation of colony amplification products by agarose gel electrophosesis (see 7th sentence of 2nd paragraph on p. 2651).

Regarding claims 1, 9, and 11, Davies et al. teach methods for the non-invasive early detection of colorectal cancer by means of mutational analysis of the genes for B-raf (entire article, especially the Title), KRAS (see 4th sentence in the 3rd paragraph on p. 952) in a sample and teach a kit (see last sentence of the 1st paragraph in the 2nd column on p. 953), characterized in that the method comprises the following steps: obtaining DNA from the sample (see 2nd paragraph on p. 949), performing an amplification reaction using primers (see 2nd paragraph on p. 949) , wherein amplification products are formed and performing a mutational analysis in the amplification products (entire article especially Figure 1).

Regarding claims 1, 9, and 11, Davies et al. teach detection of colorectal cancer and teach obtaining DNA but do not specifically teach collecting a stool sample and homogenizing the sample to obtain the DNA; do not specifically teach the APC and β-catenin genes; and do not teach sequences comprising sequences of instant SEQ ID NOs: 1-18. Davies et al. teach the ERK-MAPK pathway and other pathways (see 2nd full sentence on p. 952) but do not specifically teach a second pathway of the specifically recited genes.

Regarding claims 5 and 6, Davies et al. teach detecting mutagenic conformation by isolating and sequencing both single strands (see the section *Mutation screening* on p. 953) in a sequence electropherogram (see Figure 1) obtained from capillary electrophoresis (see Title of reference no. 23 on p. 954).

Regarding claims 1, 9, and 11, Shuber et al. teach methods for the non-invasive early detection of colon cancer or intestinal cancer precursor cells (entire publication, especially the Abstract) by means of mutational analysis of the genes for APC and other genes (see Example 3 on p. 20) in a sample, characterized in that the method comprises the following steps:
collecting a stool sample (see p. 16 line 14),
homogenizing the sample (see p. 16 line 14),
obtaining DNA from the sample (see p. 16 lines 22-33),
performing an amplification reaction in the genes for APC using primers (see Example 3 on p. 20).

Regarding claims 1, 9, and 11, Shuber et al. do not specifically teach primers consisting of sequences of instant SEQ ID NOs; 1-5 and 8-18. Shuber et al do not specifically teach kits and teach screening a plurality of genomic loci (see claim 10) but do not specifically teach pathways.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods of Salahshor et al. of

mutational analysis of the genes genes for APC, K-ras, and β-catenin by including mutational analysis of the B-raf gene as suggested by Ikawa et al. and Davies et al. and by collecting and homogenizing a stool sample as suggested by Shuber et al. with a reasonable expectation of success. The motivation to do so is provided by Ikawa et al. and Davies et al., who as with Salahshor, teach detection of cancer and colorectal cancer by mutational analysis of ras genes; who teach that there is no activation of these ras genes in more than half the human tumors (see 1st sentence on p. 2651 of Ikawa et al.); and further teach that the mutational analysis of the B-raf oncogene thus improves the detection of cancer (see 1st paragraphs of both Ikawa et al. and Davies et al.). The motivation to use stool as sample is provided by Shuber et al. who teach that using stool for detection of colon cancer is an exemplary method for dectection of colon cancer (see p. 16 lines 3). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Regarding claims 1, 9, 11, and 14 as shown in Table 1 (see Office Action mailed on 05/26/2009) the references disclose sequences comprising the claimed nucleic acid sequences of SEQ ID NOs: 1-18 as summarized below. Except that, Coste et al. specifically teach the nucleic acid sequence consisting of the claimed sequence of SEQ ID NO: 13.

1-5, 8, 10, and 16	Kmiec et al. (WO200173002 published 2001),
6 and 7	Shuber et al. (WO200118252 published 2001),

11 and 12	Ferrie et al. (GB2327497 published 1999),
13	Coste et al. (1998),
14	Nollet et al. (1996 and referenced by Coste et al.),
9 and 15	Albertsen et al. (United States Patent 6,114,124 issued 2000), and
17 and 18	Ikawa et al. (1988).

Claims 1, 9, and 14 are rejected for SEQ ID NOs: 1-18, as described following. With regard to claims 1, 4-6, 9, and 14, Kmiec et al., Shuber et al. Ferrie et al., Coste et al., Nollet et al., Albertsen et al., and Ikawa et al. disclose amplification of DNA with primers designed for amplification of genes containing mutations linked to colorectal cancer.

Kmiec et al., Shuber et al., Ferrie et al., Coste et al., Nollet et al., Albertsen et al., and Ikawa et al. expressly disclose the identical nucleic acid sequences presented in SEQ ID NO: 1-18 of the instant disclosures as given above. It is noted that the instant primer sites of SEQ ID NOs: 1-12 and 14-18 are contained within the sequence disclosed by Kmiec et al., Shuber et al., Ferrie et al., Nollet et al., Albertsen et al., and Ikawa et al. Coste et al. specifically teach the sequence consisting of the claimed sequence of SEQ ID NO: 13.

The above described references with exception of Coste et al. do not specifically disclose the identical primer sequences of SEQ ID NOs: 1-12 and 14-18, the primers used in the claimed invention. Coste et al. specifically teach the sequence consisting of the claimed sequence of SEQ ID NO: 13.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers of the amplification of genes associated with colorectal cancer and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck et al (1999) expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer

functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

Furthermore as given above, at least Salahshor et al., Ikawa et al., Davies et al., and Shuber et al. provide the motivation to perform amplification of the known genes for APC, K-ras, β-catenin, and B-raf for the detection of colorectal cancer. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Further motivation to perform mutational analysis on genes of multiple pathways including the Ras and APC pathway is provided by the teachings of McCormick as follows.

Regarding claims 1 and 9, McCormick teaches a first Ras pathway where genes for the first pathway are ras and raf (see Figure 1) and a second APC pathway where genes for the second pathways are APC and β--catenin (see Figure 2).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods and kits of Salahshor et al., Davies et al., Kmiec et al., Shuber et al. (2001), Ferrie et al., Coste et al., Nollet et al., Albertsen et al., Ikawa et al., and Buck et al. by determining the existence of mutations in the ras, raf, APC and β-catenin in the RAS pathway and APC pathway respectively as suggested by McCormick with a reasonable expectation of success. The motivation to do so is provided by McCormick who teach the importance of determing mutations in the genes of these two pathways for detection of cancer including colon cancer:

> "Here, I review some of these issues in the context of two major pathways that are misregulated in human cancers at high frequencies: the Ras pathway and the adenomatous polyposis coli (APC) pathway" (see last sentence of the 1st paragraph of text on p. M53);
>
> "We now know that oncogenes and tumour suppressors depend on one another for their selective advantage, and that they affect multiple pathways that intersect and overlap. The interactive nature of each genetic change has important implications for cancer therapy and for the stepwise model of carcinogenesis" (see Abstract); and
>
> " Mutational inactivation of the gene encoding APC occurs in the majority of human colon cancers and leads to accumulation of β-catenin" (see 1st sentence of the 2nd paragraph on p. M54).

Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Stratagene catalog provides a further motivation to combine reagents into kit format (page 39). It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the reagents of the methods of Salahshor et al., Davies et al., Kmiec et al., Shuber et al. (2001), Ferrie et al., Coste et al., Nollet et al., Albertsen et al., Ikawa et al., McCormick, Buck et al. into a kit format as discussed by Stratagene catalog since the Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. Thus one need not purchase gram quantities of 10 different reagents, each of which is needed in only microgram amounts, when beginning a series of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually far more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantities you will actually need, premixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control" (page 39, column 1).

22. Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Salahshor et al., Davies et al., Kmiec et al., Shuber et al. (2001), Ferrie et al., Coste et al., Nollet

et al., Albertsen et al., Ikawa et al., McCormick, Buck et al., and Stratagene as applied to claim 1 above, and further in view of Gerry et al. (1999).

Salahshor et al., Davies et al., Kmiec et al., Shuber et al. (2001), Ferrie et al., Coste et al., Nollet et al., Albertsen et al., Ikawa et al., McCormick, Buck et al., and Stratagene teach as noted above.

Salahshor et al., Davies et al., Kmiec et al., Shuber et al. (2001), Ferrie et al., Coste et al., Nollet et al., Albertsen et al., Ikawa et al., McCormick, Buck et al., and Stratagene do not specifically teach methods using DNA chips.

Regarding claim 2, Gerry et al. teach methods characterized in that the detection of mutations in selected sections of the genes for K-ras and other genes is effected by means of a DNA chip which is a DNA microchip, said DNA chip including probes for K-ras (entire article, especially the Abstract)

Regarding claim 2, Gerry et al. teach methods for detection of the K-ras gene and other genes but does not specifically teach detection of the genes of APC, β-catenin, and B-raf and do not specifically teach the primers of claim 1.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods of Salahshor et al., Davies et al., Kmiec et al., Shuber et al. (2001), Ferrie et al., Coste et al., Nollet et al., Albertsen et al., Ikawa et al., McCormick, Buck et al., and Stratagene by using DNA microchips as suggested by Gerry et al. with a reasonable expectation of success. The

motivation to do so is provided by Gerry et al. who teach: "Thus, a single array design can be programmed to detect a wide range of genetic mutations. Robust methods for the rapid detection of mutations at numerous potential sites in multiple genes hold great promise to improve the diagnosis and treatment of cancer patients" (see 1st two full sentences on p. 259). Furthermore Gerry et al. teach the methods are applicable to known multiple genes and specifically to the K-ras gene, and as Salahshor et al., Davies et al., Kmiec et al., Shuber et al., Ferrie et al., Coste et al., Nollet et al., Albertsen et al., Ikawa et al., and Buck et al. in combination teach detection of the known multiple genes of APC, K-ras, β-catenin, and B-raf; it would have been obvious to one of ordinary skill in the art at the time of claimed invention to use the DNA microchip methods of Gerry et al. for detection of the known multiple genes of APC, K-ras, β-catenin, and B-raf. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

23. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Salahshor et al., Davies et al., Kmiec et al., Shuber et al. (2001), Ferrie et al., Coste et al., Nollet et al., Albertsen et al., Ikawa et al., McCormick, Buck et al., and Stratagene as applied to claim 1 above, and further in view of Shuber et al. (WO199858081 published 1998).

Salahshor et al., Davies et al., Kmiec et al., Shuber et al. (2001), Ferrie et al., Coste et al., Nollet et al., Albertsen et al., Ikawa et al., McCormick, Buck et al., and Stratagene teach as noted above.

Salahshor et al., Davies et al., Kmiec et al., Shuber et al. (2001), Ferrie et al., Coste et al., Nollet et al., Albertsen et al., Ikawa et al., McCormick, Buck et al., and Stratagene do not specifically teach methods using magnetic beads.

Regarding claim 3, Shuber et al. (1998) teach methods characterized in that the K-ras and other genes are accumulated from total DNA by hybridizing sequence-specific biotinylated oligonucleotides with the genes for K-ras (see p. 6 lines 24 and 25 for capture of the kras gene) using coupling of the biotin residue to streptavidin and subsequent separation via magnetic particles (see p. 5 line 25 to p. 6 line 2 and see entire p. 9).

Regarding claim 3, Shuber et al. (1998) teach methods for detection of the K-ras gene and other genes but does not specifically teach detection of the genes of APC, β-catenin, and B-raf and do not specifically teach the primers of claim 1.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods of Salahshor et al., Davies et al., Kmiec et al., Shuber et al. (2001), Ferrie et al., Coste et al., Nollet et al., Albertsen et al., Ikawa et al., McCormick, Buck et al., and Stratagene by using biotinylated probes with streptavidin coated magnetic beads as suggested by Shuber et al. (1998) with a reasonable expectation of success. The motivation to do so is provided by Shuber et al. (1998) who teach that these methods produce increased yields of DNA from stool, thereby allowing more efficient sequence-specific capture of

target nucleic acids. Furtermore Shuber et al. (1998) teaches the methods are applicable to known genes in general and specifically to the kras gene, and as Salahshor et al., Davies et al., Kmiec et al., Shuber et al. (2001), Ferrie et al., Coste et al., Nollet et al., Albertsen et al., Ikawa et al., McCormick, and Buck et al. in combination teach detection of the known genes of APC, K-ras, β-catenin, and B-raf; it would have been obvious to one of ordinary skill in the art at the time of claimed invention to use the methods of Shuber et al. (1998) for detection of the known genes of APC, K-ras, β-catenin, and B-raf. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

24. Claims 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Salahshor et al., Davies et al., Kmiec et al., Shuber et al. (2001), Ferrie et al., Coste et al., Nollet et al., Albertsen et al., Ikawa et al., McCormick, Buck et al., and Stratagene as applied to claim 1 above, and further in view of Baba et al. (1996).

Salahshor et al., Davies et al., Kmiec et al., Shuber et al. (2001), Ferrie et al., Coste et al., Nollet et al., Albertsen et al., Ikawa et al., McCormick, Buck et al., and Stratagene teach as noted above.

Salahshor et al., Davies et al., Kmiec et al., Shuber et al. (2001), Ferrie et al., Coste et al., Nollet et al., Albertsen et al., Ikawa et al., McCormick, Buck et al., and Stratagene do not specifically teach HPLC or SSCP techniques.

Regarding claims 12 and 13, Baba et al. teach methods of detecting disease by analysis of disease causing genes including colon cancer causing genes and other genes (see Title and Table 3) including applying analysis techniques to detection of K-ras oncogene mutations (see last sentence on p. 286 continued to p. 287), teach an electophoretic technique of SSCP which is capillary electrophoresis applied to SSCP analysis of the p53 gene (see section *4.3 SSCP* on p. 287) and teach that a chromatographic procedure can be used which are reverse phase and ion-exchange HPLC (see 1st paragraph under section *5.2 Monitoring of DNA* on p. 296).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods of Salahshor et al., Davies et al., Kmiec et al., Shuber et al. (2001), Ferrie et al., Coste et al., Nollet et al., Albertsen et al., Ikawa et al., McCormick, Buck et al., and Stratagene by using an SSCP electrophorectic technique or an HPLC chromatographic procedure as suggested by Baba et al. with a reasonable expectation of success. The motivation to do so is provided by Baba et al. who teach that: "SSCP analysis using capillary electrophoresis has also been successfully applied to the detection of the mutation on K-ras oncogene . . . " (see 1st sentence of 2nd paragraph on p. 290) and can succesfull successfully detect mutations with reverse phase and ion exchange HPLC . Furthermore Baba et al. teach the methods are applicable to known genes in general and specifically to the K-ras gene, and as Salahshor et al., Davies et al., Kmiec et al., Shuber et al. (2001), Ferrie et al., Coste et al., Nollet et al., Albertsen et al., Ikawa et al., McCormick, Buck et al. in combination teach detection of the known genes of APC, K-ras, β-catenin, and B-raf; it

would have been obvious to one of ordinary skill in the art at the time of claimed invention to use the methods of Baba et al. for detection of the known genes of APC, K-ras, β-catenin, and B-raf. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Conclusion

25. No claim is free of the prior art.

26. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

27. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Staples whose telephone number is (571) 272-

9053. The examiner can normally be reached on Monday through Thursday, 9:00 a.m. to 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Mark Staples
/M. S./
Examiner, Art Unit 1637
November 24, 2009

/Teresa E Strzelecka/
Primary Examiner, Art Unit 1637
November 29, 2009